AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of all claims in the application.

Listing of Claims

1. **(Previously Presented)** A method of identifying a G protein coupled receptor (GPCR) agonist, wherein the GPCR agonist is capable of activating GPCR signaling while exhibiting reduced GPCR internalization as compared to a control compound, comprising the steps of:

(a) providing a cell comprising at least one GPCR or a modified GPCR capable of activating intracellular signaling and an arrestin, or a fragment thereof capable of binding a GPCR,

(b) exposing the cell to at least one test compound,

(c) measuring GPCR signaling at two or more points in time,

(d) measuring internalization of the GPCR at two or more points in time,

(e) quantitatively determining if GPCR internalization is reduced by comparing GPCR internalization in the presence of the test compound to GPCR internalization in the presence of a control compound, and wherein GPCR signaling is activated in the presence of the test compound as compared to GPCR signaling in the absence of the test compound,

(f) wherein a reduction in GPCR internalization in the presence of the test compound as compared to the control compound indicates the test compound is a GPCR agonist capable of activating GPCR signaling while exhibiting reduced GPCR internalization.

2. **(Canceled)**

3. **(Previously Presented)** The method of claim 1, wherein the internalization of the GPCR is measured by monitoring localization of a detectable molecule bound to the arrestin or to the GPCR.

4. **(Previously Presented)** The method of claim 1, wherein signaling is quantitated by measuring an intracellular effector, wherein said effector is cAMP, cyclic GMP, calcium, a lipid, phosphatidylinositol, a hydrogen ion, or an ion transport molecule.

5-7. **(Canceled)**

8. **(Previously Presented)** The method of claim 1, wherein the signaling is activated for a longer time period after stimulation by the test compound than the length of time of activation after stimulation by the control compound.

9. **(Previously Presented)** The method of claim 1, wherein the internalization of the GPCR is measured by determining the localization of the GPCR in the plasma membrane, pits, endosomes, endocytic vesicles, or cytosol.

10. **(Previously Presented)** The method of claim 1, wherein the GPCR is a class A, or class B receptor.

11. **(Previously Presented)** The method of claim 1, wherein the GPCR is a μ opioid, β_1AR, β_2AR, or dopamine receptor.

12. **(Previously Presented)** The method of claim 1, wherein the internalization of the GPCR is measured by visualization of a radioisotope, an epitope tag, an affinity label, an enzyme, a fluorescent group, or a chemiluminescent group attached to the arrestin or the GPCR.

13. **(Previously Presented)** The method of claim 1, wherein the signaling is measured at the same time as the internalization is measured.

14. **(Original)** The method of claim 1, wherein the cell is exposed to the compound once, and wherein the cell is not exposed a second time to the compound.

15. **(Canceled)**

16. **(Previously Presented)** The method of claim 1, wherein the GPCR is a rat, mouse, pig, or primate GPCR.

17. **(Previously Presented)** The method of claim 1, wherein the steps (a) – (f) are repeated, and wherein the GPCR used in the repeated steps is from a different species than the GPCR used in steps (a) – (f).

18. **(Previously Presented)** The method of claim 17, wherein a test compound that is used in steps (a) – (f) is not used in the repeated steps.

19. **(Previously Presented)** The method of claim 1, wherein the test compound is from a combinatorial library.

20. **(Previously Presented)** The method of claim 1, wherein the signaling in the presence of the test compound is equal to or greater than the signaling in the presence of the control compound.

21. **(Previously Presented)** The method of claim 1, wherein the method is repeated at different concentrations of compound to yield a dose-response curve for the signaling measurement and a dose-response curve for the internalization measurement in the presence of the test compound.

22. **(Previously Presented)** The method of claim 21, wherein the quantitative determination includes a comparison of the dose-response curve for the signaling measurement to the dose-response curve for the internalization measurement.

23. **(Previously Presented)** The method of claim 21, wherein a second dose-response curve for the signaling measurement and a second dose-response curve for the internalization measurement are determined in the presence of control compound.

24. **(Previously Presented)** The method of claim 23, wherein the dose-response curve for the internalization measurement in the presence of the test compound is less than the dose-response curve for the internalization measurement in the presence of the control compound.

25. **(Previously Presented)** The method of claim 23, wherein the dose-response curve for the signaling measurement in the presence of the test compound is approximately equal to or greater than the dose-response curve for the signaling measurement in the presence of the control compound.

26. **(Previously Presented)** The method of claim 24, wherein the reduced internalization is determined by a decrease in the Max of the dose-response curve for the internalization measurement in the presence of the test compound, as compared to the Max of the dose-response curve for the internalization measurement in the presence of the control compound.

27. **(Previously Presented)** The method of claim 24, wherein the reduced internalization is determined by an increase in the EC50 of the dose-response curve for the internalization measurement in the presence of the test compound, as compared to the EC50 of the dose-response curve for the internalization measurement in the presence of the control compound.

28-54. **(Canceled)**

55. **(Currently Amended)** A method of identifying a G protein coupled receptor (GPCR) agonist, wherein the GPCR agonist is capable of activating ~~TMR~~ **GPCR** signaling while exhibiting reduced ~~TMR~~ **GPCR** internalization over a control compound, comprising the steps of:

(a) providing a cell comprising at least one GPCR or a modified GPCR capable of activating intracellular signaling and an arrestin, or a fragment thereof capable of binding a GPCR,

(b) exposing the cell to at least one test compound,

(c) measuring GPCR signaling at one or more concentration of the test compound,

(d) measuring internalization of the GPCR at one or more concentration of the test compound,

(e) quantitatively determining if GPCR internalization is reduced by comparing GPCR internalization in the presence of the test compound to GPCR internalization in the presence of a control compound, and wherein GPCR signaling is activated in the presence of the test compound as compared to GPCR signaling in the absence of the test compound,

(f) wherein a reduction in GPCR internalization in the presence of the test compound as compared to the control compound indicates the test compound is a GPCR agonist capable of activating GPCR signaling while exhibiting reduced GPCR internalization.

56. **(Canceled)**

57. **(Previously Presented)** The method of claim 55, wherein the internalization of the GPCR is measured by monitoring localization of a detectable molecule bound to the arrestin or to the GPCR.

58. **(Previously Presented)** The method of claim 55, wherein signaling is quantitated by measuring an intracellular effector, wherein said effector may be cAMP, cyclic GMP, calcium, a lipid, phosphatidylinositol, a hydrogen ion, or an ion transport molecule.

59–61. **(Cancelled)**

62. **(Previously Presented)** The method of claim 55, wherein the signaling is activated for a longer time period after stimulation by the test compound than the length of time of activation after stimulation by the control compound.

63. **(Previously Presented)** The method of claim 55, wherein the internalization of the GPCR is measured by determining the localization of the GPCR in the plasma membrane, pits, endosomes, endocytic vesicles, or cytosol.

64. **(Previously Presented)** The method of claim 55, wherein the GPCR is a class A, or class B receptor.

65. **(Previously Presented)** The method of claim 55, wherein the GPCR is a μ opioid, β_1AR, β_2AR, or dopamine receptor.

66. **(Previously Presented)** The method of claim 55, wherein the internalization of the GPCR is measured by visualization of a radioisotope, an epitope tag, an affinity label, an enzyme, a fluorescent group, or a chemiluminescent group attached to the arrestin or the GPCR.

67. **(Previously Presented)** The method of claim 55, wherein the signaling is measured at the same time as the internalization is measured.

68. **(Original)** The method of claim 55, wherein the cell is exposed to the compound once, and wherein the cell is not exposed a second time to the compound.

69. **(Canceled)**

70. **(Previously Presented)** The method of claim 55, wherein the GPCR is a rat, mouse, pig, or primate GPCR.

71. **(Previously Presented)** The method of claim 55, wherein the steps (a) – (f) are repeated, and wherein the GPCR used in the repeated steps is from a different species than the GPCR used in steps (a) – (f).

72. **(Previously Presented)** The method of claim 71, wherein a test compound that is used in steps (a) – (f) is not used in the repeated steps.

73. **(Previously Presented)** The method of claim 55, wherein the test compound is from a combinatorial library.

74. **(Original)** The method of claim 55, wherein the signaling in the presence of the test compound is approximately equal to or greater than the signaling in the presence of the control compound.

75. **(Previously Presented)** The method of claim 55, wherein the method is repeated at different concentrations of compound to yield a dose-response curve for the signaling measurement and a dose-response curve for the internalization measurement in the presence of the test compound.

76. **(Previously Presented)** The method of claim 75, wherein the quantitative determination includes a comparison of the dose-response curve for the signaling measurement to the dose-response curve for the internalization measurement.

77. **(Previously Presented)** The method of claim 75, wherein a second dose-response curve for the signaling measurement and a second dose-response curve for the internalization measurement are determined in the presence of control compound.

78. **(Previously Presented)** The method of claim 77, wherein the dose-response curve for the internalization measurement in the presence of the test compound is less than the dose-response curve for the internalization measurement in the presence of, the control compound.

79. **(Previously Presented)** The method of claim 77, wherein the dose-response curve for the signaling measurement in the presence of the test compound is approximately equal to or greater than the dose-response curve for the signaling measurement in the presence of the control compound.

80. **(Previously Presented)** The method of claim 78, wherein the reduced internalization is determined by a decrease in the Max of the dose-response curve for the internalization measurement in the presence of the test compound, as compared to the Max of the dose-response curve for the internalization measurement in the presence of the control compound.

81. **(Previously Presented)** The method of claim 78, wherein the reduced internalization is determined by an increase in the EC50 of the dose-response curve for the internalization measurement in the presence of the test compound, as compared to the EC50 of the dose-response curve for the internalization measurement in the presence of the control compound.

82-108 **(Canceled)**

109. **(Previously Presented)** The method of claim 16, wherein the primate GPCR is a human GPCR.

110. **(Previously Presented)** The method of claim 70, wherein the primate GPCR is a human GPCR.